PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of: Contag *et al.*

Serial No.: 08/270,631

Group Art Unit: 1802

Filed: July 1, 1994

Examiner: Shaver, J. E.

For: NON-INVASIVE LOCALIZATION OF A LIGHT-EMITTING CONJUGATE IN A MAMMAL

Attorney Docket No.: 8678-003-999

AMENDMENT AND RESPONSE PURSUANT TO 37 C.F.R. § 1.115

Honorable Commissioner of Patents and Trademarks
Washington, D.C. 20231

Sir:

The Examiner has rejected the pending claims of the instant application in the Office Action, mailed February 8, 1996, Paper No. 10 ("Office Action"). The Office Action and the rejections and objections therein have been carefully reviewed and studied. Applicants respectfully request that the following amendments be entered in the above-referenced patent application, pursuant to 37 C.F.R. § 1.115, and request reconsideration of the application, and each of the rejections set forth in the Office Action.

Applicants enclose a petition for a one (1) month extension of time to June 8, 1996 to reply to the pending office action.

EXPRESS MAIL CERTIFICATION

"Express Mail" label No. TB 665 381 30X US Date of Deposit June 10, 1996.

I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 C.F.R. 1.10 on the date indicated above and is addressed to the Commissioner of Patents and Trademarks, Washington, D.C. 20231.

Gabriel Urquidez
(Typed or printed name of person mailing paper or fee)

(Signature of person mailing paper or fee)

THE AMENDMENTS

In The Claims:

Please amend the Claims as follows:

In Claim 1, line 2, please replace the word "in" by the phrase --from within--.

In Claim 1, line 16, please replace the phrase "constructing such an image" by --detecting said image through an opaque tissue of said mammal--.

REMARKS

Claims 1-3, 6, 8-12, and 14-16, and 20-34 are pending in this application. Claims 4-5, 7, 13, and 17-19 are drawn to a non-elected invention and have been withdrawn from consideration. Claim 1 has been amended. In the following is a brief summary of the invention.

I. The Invention

The present invention is directed to noninvasive methods and compositions for detecting, localizing and tracking entities and biological events in a mammal. The entities or biological events are conjugated/linked to a light-emitting moiety, either directly or causally, *e.g.*, as in the case that the event to be detected causes light to be emitted or attenuated from a separate molecular conjugate, and as such can be noninvasively detected through the opaque, *i.e.*, light-scattering layers, of the subject's body, *e.g.*, the skin.

For example, prior to the present invention, the ability to monitor the progression of infectious diseases was basically limited to *ex vivo* methods of detecting and quantifying infectious agents in tissue samples. The replication of an infectious agent in a host often involves primary, secondary and tertiary sites of replication. The sites of replication and the course that an infectious agent follows through these sites is determined by the route of inoculation, factors encoded by the host as well as determinants of the infecting agent.

Accordingly, it would be desirable to have a means of tracking, for example, the progression of an infection in the body of a subject. Ideally, the tracking could be done noninvasively, *i.e.*, without surgery, such that the subject could be evaluated as often as necessary without undergoing detrimental effects. Such noninvasive tracking is the objective of and addressed by the present invention.

More specifically, the invention is directed to methods and compositions for detecting and localizing light originating from a mammal. Also disclosed are methods for targeting light emission to selected regions, as well as techniques for tracking entities within the mammal. In addition, animal models for disease states are disclosed, as well as methods for localizing and tracking the progression of a disease or a pathogen within the animal, and for screening putative therapeutic compounds effective to inhibit the disease or pathogen.

II. Formal Matters

Drawings. Formal drawings in compliance with 37 CFR 1.84(a)(1) will be submitted once the Application is allowed or indicated as allowable.

III. The Amendments

The amendments to the claims have been made, without prejudice, to address the Examiner's rejections under 35 U.S.C. §102(b) and §112, second paragraph. The above-made amendments do not constitute new matter under 35 U.S.C. §132 and are fully supported by the specification.

More specifically, Claim 1 has been amended, without prejudice, in order to clarify the subject matter the Applicants consider as the invention, *i.e.*, Claim 1 now recites "[a] noninvasive method for detecting the localization of a biocompatible entity within a mammalian subject", whereby detection is through an opaque tissue of said mammal. The amendment has been made in compliance with the Examiner's suggestions (*see*, Office Action, page 8, *item 9*), in order to expedite prosecution of the application. The amendment is fully supported in the specification, for example, at page 32.

IV. Allowable Subject Matter

Applicants note that the subject matter of Claim 10 is deemed to be allowable by the Examiner if Applicants overcome the rejection under 35 U.S.C. §112. Further, the Examiner acknowledges that the ***prior art does not teach that visible light generated within an opaque body can be imaged from an outside surface, i.e., through a layer of light-scattering body substance***. She concludes and suggests, that the rejections under 35 U.S.C. §102(b) can be overcome by making proper amendments to the claims. *See*, Office Action, at page 8, *item 9*.

As discussed, *infra*, Applicants believe that the rejections under 35 U.S.C. §112, second paragraph have been properly addressed, and, further, that the 35 U.S.C. §102(b) rejections have been addressed and/or overcome by the amendments to Claim 1.

V. The Rejections

A. The Rejection Of Claims 26-50 Under 35 U.S.C. §112, Second Paragraph

The Examiner rejected Claims 1-3, 8-12, and 14-16 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter of the invention. The rejections are in part traversed and in part avoided, as discussed more fully below.

The Term "Noninvasive". The Examiner alleges that Claim 1 is unclear with respect to the term "noninvasive".

The rejection is respectfully traversed, as the term "noninvasive" would be readily understood to have its plain meaning. For example, as Merriam Webster's Collegiate Dictionary sets forth, "noninvasive" means "not involving penetration (as by surgery or hypodermic needle) of the skin of the intact organism". Thus, the unambiguous, definite meaning of the term "noninvasive" includes ***all methods which do not involve penetration of the skin***, which includes, among other diagnostic methods, endoscopy or colonscopy. Such methods are intended to be within the scope of the invention accordingly.

Furthermore, the Examiner's attention is directed to the fact that the term noninvasive as used in the claims language refers to a ***noninvasive detection procedure***, however, any other portion of the testing, may be invasive. For example, the placement of the substrate or the dosing with a treatment to test a response to the treatment may be through injection, *e.g.*, i.p. or i.v. injection; or, for specific applications, an emitter-covered plastic sensor may be placed under the skin. For example, a sensor responding to a physiological parameter could be surgically implanted in a tumor, and the light imaged externally in order to map a parameter like oxygenation, or the efficacy of a drug could be imaged noninvasively using a sensor which allows monitoring of the cure of a disease.

In view of the above arguments, Applicants respectfully request that the Examiner withdraw the rejection of Claims 1-3, 8-12, and 14-16 under 35 U.S.C. §112, second paragraph.

The Term Biocompatible. The Examiner further alleges that the meaning of the term "biocompatible" is unclear. Specifically, the Examiner objects to Claims 9 and 10 which recite that the biocompatible entity is a pathogen.

Applicants disagree with and respectfully traverse this rejection under 35 U.S.C. §112, second paragraph. Applicants submit that the term "biocompatible" is used properly and in full compliance with its definition as set forth in the specification.

More specifically, the Examiner states that a pathogen would induce a significant immune response in the body, and concludes that it is not clear that a pathogen should be considered "biocompatible". However, while the Examiner may have such understanding of the term "biocompatible", she is reminded that Applicant may be his own lexicographer, and terms are constructed according to their definition set forth in the specification.

The specification unequivocally defines a "biocompatible" entity as "an entity that can be administered to a mammal". Accordingly, any entity, living or non-living, which may be administered to a mammal, even one which causes a biological response, *e.g.*, an immune response, is intended to be within the scope of the term "biocompatible". For example, on page 13-14, the specification sets forth that "[b]iocompatible entities include, but are not limited to, small molecules such as cyclic organic molecules; macromolecules such as proteins; microorganisms such as viruses, bacteria, yeast and fungi; eukaryotic cells; all types of pathogens and pathogenic substances; and particles such as beads and liposomes. In another aspect, biocompatible entities may be all or some of the cells that constitute the mammalian subject being imaged."

Moreover, with respect to the Examiner's objection that a pathogen could be considered as "biocompatible", the specification explicitly states that a pathogen is included in this definition as it sets forth that "[t]his includes pathogens which may be deleterious to the mammal". *See*, specification, page 12-13.

In view of the above arguments, Applicants respectfully request that the Examiner withdraw the rejection of these Claims under 35 U.S.C. §112, second paragraph.

The Term "Conjugate". The Examiner objected to the term "conjugate" as used in Claim 1, stating that "conjugate" is too vague and confusing because it appears to encompass both a transformed cell, as well as an infection targeting moiety, *i.e.*, a fusion protein. The objection as to the term "conjugate" is respectfully traversed.

Applicants disagree with the Examiner's assertion that the term "conjugate" is unclear. First, the plain meaning of the term "conjugate" is well understood as "joined together". Thus, there is no reason why a "conjugate" of a biocompatible entity and a light-emitting moiety could not encompass both a transformed cell ***and*** a fusion protein.

Second, Applicants submit that what is meant with the phrase "conjugate" is clearly defined in the specification. Applicants wish to remind the Examiner that a term used in the claims language is constructed in accordance with its description and definition set forth in the specification; as set forth in the MPEP, the meaning of a term "should be apparent from the descriptive portion of the specification with clear disclosure as to its import. MPEP 608.01(o).

With respect to the term "conjugate", the specification of the subject invention clearly states:

> The moiety may be conjugated to the entity by a variety of techniques, including incorporation during synthesis of the entity (*e.g.*, chemical or genetic, such a fusion protein of an antibody fragment and a light-generating protein), chemical coupling post-synthesis, non-covalent association (*e.g.*, encapsulation by liposomes), *in-situ* synthesis in the entity (*e.g.*, expression of a heterologous bioluminescent protein in a transformed cell), or *in situ* activatable promoter-controlled expression of a bioluminescent protein in cells of a transgenic animal stimulated by a promoter inducer (*e.g.*, interferon-activated promoter stimulated by infection with a virus). (emphasis added).

See, specification, at page 2.

Thus, clearly and unambiguously, the specification states that a biocompatible entity (as defined in the specification, *see*, *supra*) and a light-generating moiety may be conjugated by a number of techniques, *e.g.*, by formation of a fusion protein, or by expression of a heterologous protein in a transformed cell. Accordingly, it will be well understood that the term "conjugate" encompasses transformed cells as well as any kind of fusion protein. There is no reason why the term conjugate cannot both, since, as pointed out above, the patentee may be his own lexicographer.

In view of the above arguments, Applicants respectfully request that the Examiner withdraw the objection to the clarity of the term "conjugate" under Section 112, second paragraph.

B. The Rejection Of Claims 1-3, 6, 8-9, 11-12, and 14-16 Under 35 U.S.C. §102(b)

The Examiner rejected Claims 1-3, 6, 8-9, 11-12, and 14-16 Under 35 U.S.C. §102(b) as being anticipated by several references.

First, the Examiner rejected Claims 1-3, 6, 8-9, and 16 under 35 U.S.C §102(b) as being anticipated by Kuhn *et al.*, 1991, *Arch. Surg.* 126:1398-1403 ("Kuhn").

Second, the Examiner rejected Claims 1-3, 6, 8, and 11 under 35 U.S.C §102(b) as being anticipated by Compton *et al.*, 1990, U.S. Patent No. 4,912,031 ("Compton").

Third, the Examiner rejected Claim 1-3, 6, 8-9, and 16 under 35 U.S.C §103(b) as being anticipated by Horan *et al.*, 1988, U.S. Patent No. 4,762,701 ("Horan").

Fourth, the Examiner rejected Claims 1-3, 8, 11-12, and 14-16 under 35 U.S.C §102(b) as being anticipated by Tamiya *et al.*, 1990, *Nucleic Acids Res.* 18:1072 ("Tamiya").

The rejections are in part believed to be avoided by the amendment to the claims, and in part traversed.

More specifically, and with respect to the points raised in the Office Action, Applicant offers the following remarks:

1. Amended Claims 1-3, 6, 8-9, And 16 Are Not Anticipated By And Are Patentable Over Kuhn

The Examiner rejected Claims 1-3, 6, 8-9, and 16 under 35 U.S.C §102(b) as being anticipated by Kuhn. Applicant respectfully traverses this rejection.

The Examiner is respectfully reminded that the standard governing anticipation under 35 U.S.C. §102 is one of strict identity. In fact, the Court of Appeals for the Federal Circuit has enunciated the long settled law concerning anticipation under 35 U.S.C. § 102: anticipation can only be established by a single prior art reference which discloses ***each and every element*** of the claimed invention; anticipation is not shown even if the differences between the claims and the prior art references are argued to be "insubstantial" and the missing elements could be supplied by the knowledge of one

skilled in the art. Structural Rubber Prod. Co. v. Park Rubber Co., 221 U.S.P.Q. 1264 (Fed. Cir. 1984). Furthermore, in Jamesbury Corp. v. Litton Industrial Products, Inc., 225 U.S.P.Q. 253 (Fed. Cir. 1985) the court pointed out that the assertion of invalidity for lack of novelty is erroneous if the prior art disclosed "substantially the same thing". The prior art references in question must meet each claim limitation in order to constitute anticipation.

The Section 102 rejection based upon Kuhn must fail as a matter of law, because ***Kuhn does not disclose each and every element of the claimed invention.***

The Examiner correctly observes that Kuhn discloses ***radioimmunodetection*** using monoclonal antibodies directed against a tumor-associated antigen as a means for the external imaging of metastatic deposits in patients suspected to have recurrent colorectal cancer. As means for detection, Kuhn uses γ-radiation, *i.e.*, radiation in the ***non-visible*** range (pico meter (pm)-range). In support of her rejection, the Examiner mistakenly contends that the term "light" may be interpreted as any form of electromagnetic radiation; on this basis she concludes that Kuhn anticipates the present invention. *See*, Office Action, page 4.

However, this allegation is mistaken in view of the specification of the present invention. As specifically set forth in the specification, the term ***"light", in the meaning of the subject invention, is defined as electromagnetic radiation within the visible or near-visible range***. Particularly, the specification sets forth:

> Light is defined herein, unless stated otherwise, as electromagnetic radiation having a wavelength of between about 300 nm and about 1100 nm. (emphasis added).

See, specification, at page 13.

Thus, as clearly and unambiguously set forth in the specification, the light-generating moieties, as presently claimed, emitting light at a wave-length of about 300 to about 1100 nm do not encompass radioactive radiation, which emits electromagnetic waves of a wave-length in the pico meter-range. Accordingly, Kuhn cannot anticipate the claimed invention.

In view of the above arguments, Claims 1-3, 6, 8-9, and 16 are not, as a matter of fact and law, anticipated by Kuhn cited by the Examiner, and Applicants respectfully request withdrawal of the rejections under 35 U.S.C §102(b).

2. Amended Claims 1-3, 6, 8, And 11 Are Not Anticipated By And Are Patentable Over Compton

The Examiner rejected Claims 1-3, 6, 8, and 11 under 35 U.S.C §102(b) as being anticipated by Compton. This rejection is believed to be avoided in view of the amendments to Claim 1.

Compton discloses a method for distinguishing between carcinomatous and/or precarcinomatous colo-rectal disease and histologically similar conditions effected by diseases that are not carcinomatous or precarcinomatous. The disclosed method is based on the detection of an antigen, namely the blood group substance H, which is specifically associated with dysplasia in adenomatous colo-rectal polyps. More specifically, a fluorescent, radiolabelled, or phosphorescent antibody is introduced into the evacuated colon. After sufficient incubation time, unbound antibody is washed off, and binding of the labelled antibody to the colonic epithelium is determined by colonscopy. Thus, while the method disclosed is noninvasive, *i.e.*, no penetration of the skin is required (*see, supra*), the diagnostic antibodies are bound to and detected on a surface, *i.e.*, the colonic epithelium. The present claims, as amended, in contrast, are directed to the detection of a biocompatible entity <u>through an opaque, *i.e.*, light-scattering tissue</u> of a mammalian subject.

Accordingly, Claims 1-3, 6, 8, and 11, as amended, are not anticipated by Compton and Applicants respectfully request that the Examiner withdraw the rejections under 35 U.S.C §102(b).

3. Amended Claims 1-3, 6, 8-9, And 16 Are Not Anticipated By And Are Patentable Over Horan

The Examiner rejected Claims 1-3, 6, 8-9, and 16 under 35 U.S.C §102(b) as being anticipated by Horan. This rejection is believed to be avoided in view of the amendments to Claim 1.

Horan discloses a method for tracking cells *in vivo* and for determining *in vivo* cell life time. More specifically, cells are labelled with cyanine dyes, which may be detected

by measuring fluorescence. While the reference discloses that fluorescence may be used to track and detect cells in areas which are visible from the outside of the body (*e.g.*, macula, retina, blood vessels of the eye), it does not teach the detection of a biocompatible entity through an opaque, *i.e.*, light-scattering tissue of a mammalian subject, as presently claimed.

Accordingly, Claims 1-3, 6, 8-9, and 16, as amended, are not anticipated by Horan and Applicants respectfully request that the Examiner withdraw the rejections under 35 U.S.C §102(b).

4. Amended Claims 1-3, 8, 11-12, And 14-16 Are Not Anticipated By And Are Patentable Over Tamiya

The Examiner rejected Claims 1-3, 8, 11-12, and 14-16 under 35 U.S.C §102(b) as being anticipated by Tamiya. This rejection is believed to be avoided in view of the amendments to Claim 1.

Tamiya discloses a method of continuous monitoring gene expression during embryonic development in MEDAKA embryos using the bioluminescent firefly luciferase. While Tamiya's method, as the Examiner correctly observes, is noninvasive, Tamiya explicitly states that its method relies on the fact that MEDAKA embryos are ***transparent***. The amended claims of the present invention, in sharp contrast, are directed to the detection of biocompatible entities through an opaque, *i.e.*, light-scattering tissue of a mammalian subject.

Accordingly, Claims 1-3, 8, 11-12, and 14-16, as amended, are not anticipated by Tamiya, and Applicants respectfully request withdrawal of the rejections under 35 U.S.C §102(b).

CONCLUSION

In view of the foregoing amendments and arguments, Applicants submit that the present application is believed to be in condition for allowance and an early action for that effect is respectfully requested by Applicants.

Applicants believe that no fee is due with the submission of this response. However, if any fee is required, please charge the required fee to Pennie & Edmonds Deposit Account No. 16-1150. A copy of this sheet is enclosed.

Respectfully submitted,
PENNIE & EDMONDS

Dated: June 10, 1996

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PEMP-56760.1